characteristics that these putative transporters would have to display if they existed. As stated in our earlier contribution our analysis leads us to conclude that these transporters should be equilibrative, should display K_m values in the low millimolar range, and in the case of highly-permeable drugs should show high expression coupled with high K_{cat} values. In addition, they should preferably be expressed in both apical and basolateral membranes, or have a kinetically similar partner expressed in the opposite membrane.

Thus, we maintain our conclusion that, given the data available for human ATP-binding cassette (ABC) transporters and solute carriers (SLCs), it is unlikely that these transporters account for all observations of cellular drug flux. That said, an increased understanding of drug transport kinetics emanating from studies such as [1,3] and novel experimental techniques [17] will undoubtedly lead to the identification of many new transporter functions and substrates in the coming years.

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Letter

Response to 'The Need for Speed', by Matsson *et al.*

Pedro Mendes,[1,2,3,4] Stephen G. Oliver,[5,6] and Douglas B. Kell[2,3,7,@,*]

We do not really understand the continuing failure of Matsson and colleagues to recognise where the crucial arguments lie. The chief experimental technique of interest varies transporter expression as an independent variable, and measures the consequent effects on fluxes [1]. In a recent example of this, Superti-Furga and colleagues knocked out the gene encoding the SLC35F2 transporter, thereby abolishing ~99.5% of the uptake of an anticancer drug called sepantronium bromide [2]. Thus any remaining transbilayer flux would be 0.5% at most, which we consider really is negligible, and even that 0.5% is almost certainly carried by other transporters (OCTs) previously considered to be the main transporters [2]. There is no dodging these kinds of data, nor any of many other self-consistent examples that we have reviewed in our *TiPS* paper [3] and elsewhere [4–13]. We urge readers to consider these arguments in the round. They also provide very simple explanations for why there is a blood–brain barrier, for instance, on the basis that it simply lacks the relevant transporters, with any background phospholipid bilayer diffusion clearly being negligible. This is why it is seen as a 'barrier'.

Some very brief comments of the letter of Matsson and colleagues: (i) the ludicrously high stirring rates for the propranolol and verapamil values chosen (not of course mimicked in the gut) mean that these values are complete outliers [3]; when the fuller literature for multiple drugs is considered the median rate of drug uptake into Caco-2 cells is almost two orders of magnitude lower [14], and thus easily accounted for solely by transporters; (ii) the 42% is for five transporters, mimicking the case used by Matsson *et al.*, who recognised that multiple transporters were likely involved. There is no 'mistake'. (iii) The Haldane relation is a thermodynamic relation and thus deals with state variables; the numbers of membranes that may be involved (and any mechanistic considerations at all) are thus completely irrelevant. Thermodynamics is like that.

The 'transporters-only' view has many testable (and tested) predictions, all of which have withstood scrutiny. It also admits the possibility of selective drug targeting. With attrition rates running at 92%, the pharmaceutical industry needs to ensure that it is armed with the best possible intellectual understanding of how drugs enter cells. Hence the recent 'call to arms' for research on drug transporters [15].

Update

Although they choose not to cite any of our prior literature, it seems that the first author does in fact believe that 'Transport proteins are important mediators of cellular drug influx and efflux and play crucial roles in drug distribution, disposition and clearance' [16].

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Forum

New Insights into the Epithelial-to-Mesenchymal Transition in Cancer

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The role of the epithelial-to-mesenchymal transition (EMT) in cancer progression is a long-debated issue. Recent evidence shows that EMT is not a prerequisite for cancer metastasis, but does confer chemoresistance. Future studies are needed to profile EMT events in different cancer types and under different circumstances to explore their potentials as therapeutic targets.

Controversies over the roles of EMT in cancer progression

The roles of EMT (Box 1, Figure 1) in cancer progression have been long debated. A popular proposal is that cancer cells undergo EMT to facilitate invasion and dissemination, and then go through a reverse process, termed the mesenchymal–epithelial transition (MET), for clonal outgrowth at metastatic sites [1]. However, this EMT–MET proposal is mainly based on evidence from manipulated expression of EMT-inducing transcription factors (EMT-TFs) or xenograft experiments [1,2]. Whether these experiments can faithfully recapitulate the real role of spontaneous EMT in cancer progression remains a question because the artificially activated EMT-TFs may have roles in metastasis beyond EMT activation [2]. Other evidence that lends support to the significance of EMT in cancer metastasis includes the fact that EMT can confer to cancer cells resistance to apoptosis and can endow malignant epithelial cells with cancer stem cell (CSC)-like properties [3–5]. It is appealing to assume that increased resistance to apoptosis may help cancer cells survive the rigorous journey from primary sites to distance organs and that CSC-like properties may facilitate metastatic colonization. However, direct evidence of the functionalities of naturally occurring EMT in spontaneous cancer progression is lacking, due largely to the technological difficulties of distinguishing mesenchymal cancer cells from surrounding stromal cells and of capturing and tracing the transitory EMT process *in vivo* during cancer metastasis. Therefore, controversies still exist regarding the roles of EMT in cancer progression.

New Insights into the Roles of EMT in Cancer Progression

Recent evidence sheds new light on this long-contested issue. To address the difficulties of tracing reversible EMT *in vivo*, Fischer *et al.* [6] engineered cancer cells to express a Cre-switchable fluorescent marker so that the expression of red fluorescent protein (RFP) can be switched to green fluorescent protein (GFP) upon the activation of mesenchymal-specific markers, such as fibroblast-specific protein 1 (*Fsp1*) or *vimentin*. When cells harboring this system go through EMT, they are switched from RFP^+ to GFP^+. This is an irreversible tracing system, in that EMT cells remain GFP^+ even if they return to the epithelial state afterwards. In two separate mouse models of breast cancer with